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Impact of Routine Infant BCG Vaccination on COVID-19

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SUMMARY

Objectives: In Japan, the first case of coronavirus disease 2019 (COVID-19) was diagnosed on January 15, 2020 and subsequent infections rapidly increased. The Bacillus Calmette-Guérin (BCG) vaccination program is the principal element of tuberculosis control in Japan. We investigated the impact of routine infant BCG vaccination on prevention of local COVID-19 spread.

Methods: Data on the prevalence of SARS-CoV-2 infection, annual routine infant BCG vaccine coverage (represented by the number of BCG vaccinations per live births), and other candidate factors in each prefecture were obtained from the official notifications database in Japan. We analysed the association of vaccine coverage with the prevalence of SARS-CoV-2 infection.

Results: The BCG vaccine coverage in 1999–2002, 2004, and 2012 in five prefectures with no COVID-19 infections was significantly higher than that in five prefectures with a high prevalence of infections (Mann-Whitney U test, $p<0.05$). The prevalence of SARS-CoV-2 infection was significantly negatively correlated with BCG vaccine coverage in 2004 and was significantly positively correlated with age groups 20–34 and 40–54 years (Spearman's rank correlation, $p<0.01$).

Conclusions: Our findings suggest that routine infant BCG vaccination coverage in young generation had a significant impact on prevention of local COVID-19 spread in Japan.

Introduction

In Japan, the first case of coronavirus disease 2019 (COVID-19) was diagnosed in Kanagawa Prefecture on January 15, 2020.[1] Because of an explosive increase in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections since late March, the Japanese Prime Minister declared a state of emergency for seven prefectures on April 7 and for the whole country on April 16. Japan lifted its nationwide state of emergency on May 25, 2020. The cumulative number of COVID-19 cases in Japan had topped 16,623 (13.1 per 100,000 population) on that date; however, this figure was much lower than that in Western countries.

Based on the possible effect of the Bacillus Calmette-Guérin (BCG) vaccination to prevent nonspecific infections other than tuberculosis, several clinical trials have been initiated with the aim to protect health care personnel and older people from COVID-19 infection.[2,3] Japanese bacteriologist Kiyoshi Shiga introduced BCG to Japan in 1924. The 172nd passage from the first culture is the origin of the Japanese routine infant BCG vaccine (Tokyo-172).[4] The BCG vaccination program has been the principal element in tuberculosis control in Japan for more than 70 years.

Here, we investigated the degree of impact of BCG vaccination on local prevalence of patients with COVID-19 infection, SARS-CoV-2 polymerase chain reaction-positive (PCR+) individuals, and deaths owing to COVID-19 in prefectures of Japan. Data on the number of BCG vaccinations, number of live births, and other candidate factors in each prefecture were obtained from the official notifications database of the Japanese government.[5]

Materials and methods

Prevalence of patients with COVID-19, SARS-CoV-2 PCR+ individuals, and deaths in each prefecture

Anonymous data on the number of patients with COVID-19 from January 15 to March 29, 2020, and thereafter the number of SARS-CoV-2 PCR+ individuals and the number of deaths owing to COVID-19 among Japanese residents in each prefecture were obtained from official notification records of the Ministry of Health,

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Labour and Welfare of Japan.[1] Data on March 29, April 24, and May 1, 2020 were used. Passengers aboard the Diamond Princess cruise ship anchored in Yokohama were not included. Crude SARS-CoV-2 prevalence in each prefecture was calculated as the number of patients/PCR+ individuals divided by the number of individuals in each prefecture in 2018, estimated using the results of the national census in 2010 and in 2015 taken by the Statistics Bureau, Ministry of Internal Affairs and Communications of Japan.[5]

BCG vaccination

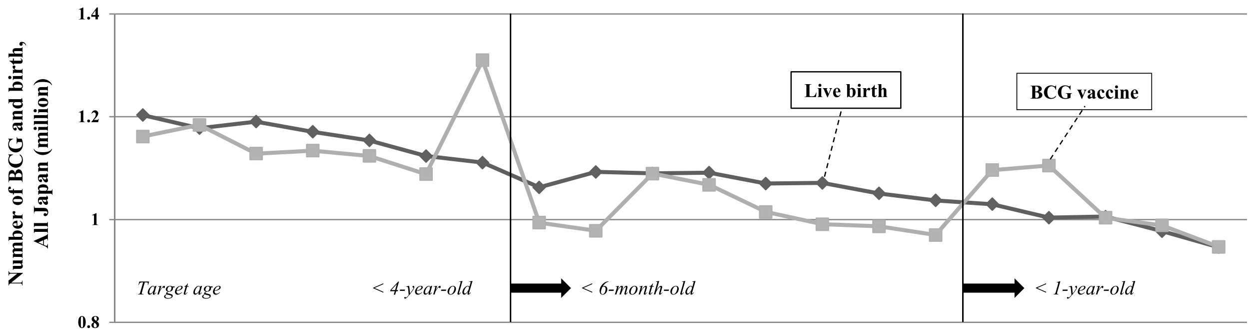
Information on the annual number of routine infant BCG vaccinations in each prefecture from 1998 to 2017 was obtained from the Report on Regional Public Health Services and Health Promotion Services, and the annual number of live births in each prefecture in the same year was obtained from the latest version of the Vital Statistics; their ratio was used as a surrogate for BCG vaccine coverage. These surveys were conducted by the Vital, Health and Social Statistics Office, Ministry of Health, Labour and Welfare of Japan.[5]

Other factors

We investigated other candidate factors related to the spread of SARS-CoV-2. The number of days from diagnosis of the first patient with COVID-19 infection in each prefecture up to March 29, 2020 was obtained from official notification records.[1] The elderly population in 2018 and the population by 5-year age groups in 2019 in each prefecture was calculated based on official population estimates.[5] The populations that migrated to and from each prefecture in 2018 was obtained from the annual report on internal migration in Japan derived from the basic resident registration; inhabitable area was calculated using data of the Statistics Bureau, Ministry of Internal Affairs and Communications.[5] The ratio of day- to night-time population, ratio of households of 5 individuals or more to

Table 1
Prevalence of patients with COVID-19, SARS-CoV-2 PCR+ individuals, and deaths in each prefecture.

	Prevalence (per million)					Deaths/PCR+ (%)	
	Patients with COVID-19 on Mar 29	PCR+ on Apr 24	Deaths on Apr 24	PCR+ on May 1	Deaths on May 1	On Apr 24	On May 1
All Japan	14.39	99.57	1.95	108.99	2.28	1.96	2.09
Hokkaido	33.30	106.32	4.73	137.34	4.92	4.45	3.58
Aomori	5.54	17.42	0	20.59	0	0	0
Iwate	0	0	0	0	0	–	–
Miyagi	0.86	36.27	0	38.00	0	0	0
Akita	4.08	16.31	0	16.31	0	0	0
Yamagata	0	60.55	0	62.39	0	0	0
Fukushima	1.07	35.41	0	38.63	0	0	0
Ibaraki	5.56	54.57	2.09	56.31	2.09	3.82	3.70
Tochigi	6.17	27.24	0	27.75	0	0	0
Gunma	9.22	71.72	4.61	74.80	7.68	6.43	10.27
Saitama	11.32	104.64	2.05	115.01	2.05	1.96	1.78
Chiba	25.58	122.78	2.88	128.86	3.68	2.34	2.85
Tokyo	31.54	271.09	1.37	298.08	1.37	0.51	0.46
Kanagawa	11.66	99.38	2.62	109.19	3.38	2.63	3.09
Niigata	13.80	28.94	0	33.39	0	0	0
Toyama	0	155.24	2.86	180.95	2.86	1.84	1.58
Ishikawa	7.87	194.23	4.37	218.72	5.25	2.25	2.40
Fukui	16.80	155.04	6.46	157.62	9.04	4.17	5.74
Yamanashi	4.90	62.42	0	63.65	0	0	0
Nagano	3.88	32.48	0	31.99	0	0	0
Gifu	10.52	73.11	3.51	73.11	3.51	4.79	4.79
Shizuoka	1.09	16.12	0	18.58	0	0	0
Aichi	22.16	62.89	3.98	64.48	4.11	6.33	6.38
Mie	5.03	25.13	0.56	25.13	0.56	2.22	2.22
Shiga	4.25	65.86	0.71	67.99	0.71	1.08	1.04
Kyoto	17.75	110.38	2.70	121.96	3.47	2.45	2.85
Osaka	23.71	164.30	2.84	181.44	4.20	1.73	2.31
Hyogo	24.07	110.32	3.10	117.07	3.10	2.81	2.65
Nara	8.22	56.76	0.75	61.24	0.75	1.32	1.22
Wakayama	18.18	55.61	1.07	64.17	2.14	1.92	3.33
Tottori	0	5.36	0	5.36	0	0	0
Shimane	0	23.53	0	33.82	0	0	0
Okayama	1.58	10.54	0	12.12	0	0	0
Hiroshima	2.13	50.41	0.35	54.31	0.35	0.70	0.65
Yamaguchi	4.38	22.63	0	23.36	0	0	0
Tokushima	1.36	6.79	0	6.79	0	0	0
Kagawa	1.04	29.11	0	29.11	0	0	0
Ehime	2.96	34.76	2.22	34.76	2.22	6.38	6.38
Kochi	19.83	100.57	2.83	104.82	4.25	2.82	4.05
Fukuoka	4.31	114.35	2.94	125.12	3.33	2.57	2.66
Saga	1.22	39.07	0	46.40	0	0	0
Nagasaki	1.49	11.93	0.75	12.68	0.75	6.25	5.88
Kumamoto	5.69	24.47	0.57	26.75	0.57	2.33	2.13
Oita	24.48	52.45	0.87	52.45	0.87	1.67	1.67
Miyazaki	2.78	15.73	0	15.73	0	0	0
Kagoshima	0.62	6.20	0	6.20	0	0	0
Okinawa	5.52	91.85	2.76	97.38	2.76	3.01	2.84



Year	Prevalence[a]	1998	1999*	2000*	2001*	2002*	2003	2004*	2005	2006	2007	2008	2009	2010	2011	2012*	2013	2014	2015	2016	2017
All Japan		0.965	1.005	0.948	0.969	0.974	0.969	1.179	0.936	0.895	1.000	0.978	0.948	0.925	0.939	0.935	1.064	1.101	0.998	1.012	1.001
Iwate	0	0.970	1.036	0.966	0.989	1.024	0.997	1.469	0.472	0.722	0.991	0.994	0.833	1.045	0.950	0.967	0.981	1.017	0.997	1.009	1.003
Yamagata	0	0.991	0.950	1.022	1.000	1.039	1.046	1.209	1.034	0.986	0.995	0.991	1.004	0.490	0.995	0.968	1.140	1.231	1.004	1.025	0.983
Toyama	0	0.891	0.701	0.668	0.712	0.693	1.044	1.399	1.908	0.916	0.916	0.984	0.998	0.851	0.981	0.987	1.032	1.044	1.004	1.023	0.993
Tottori	0	1.014	1.149	0.930	0.650	1.009	0.657	1.195	1.027	0.980	0.880	0.553	0.979	1.000	0.990	0.955	1.043	1.116	0.987	1.011	1.000
Shimane	0	0.956	1.037	0.931	1.023	0.982	1.071	1.386	1.007	1.104	0.972	1.009	0.973	0.979	0.916	0.961	1.128	1.174	0.990	1.015	1.000
Mean		0.964	0.975	0.903	0.875	0.949	0.963	1.332	1.090	0.942	0.951	0.906	0.957	0.873	0.966	0.968	1.065	1.116	0.996	1.017	0.996
SD		0.042	0.151	0.122	0.160	0.130	0.155	0.110	0.462	0.125	0.045	0.177	0.063	0.202	0.030	0.011	0.060	0.079	0.007	0.006	0.007
Hyogo	24.07	1.006	0.681	0.650	0.493	0.469	1.016	1.146	1.000	0.902	1.010	0.983	0.839	0.953	0.958	0.948	1.018	1.024	1.006	1.006	1.018
Oita	24.48	0.944	0.694	0.473	0.422	0.681	1.009	1.275	0.501	0.968	0.960	0.902	0.972	0.925	0.912	0.913	1.024	1.075	0.960	0.994	0.965
Chiba	25.58	0.928	0.835	0.778	0.736	0.731	1.003	1.169	0.862	0.860	0.978	0.999	1.006	0.869	0.976	0.943	1.031	1.048	1.016	1.030	1.018
Tokyo	31.54	0.945	0.336	0.289	0.342	0.285	0.923	0.952	0.898	0.926	0.950	0.989	0.983	0.999	0.920	0.904	1.107	1.088	0.973	0.998	0.989
Hokkaido	33.30	0.932	0.649	0.552	0.528	0.500	0.953	1.099	0.953	0.828	0.984	0.988	0.975	0.914	1.005	0.894	0.986	1.100	0.990	1.011	0.990
Mean		0.951	0.639	0.548	0.504	0.533	0.981	1.128	0.843	0.897	0.976	0.972	0.955	0.932	0.954	0.920	1.033	1.067	0.989	1.008	0.996
SD		0.028	0.164	0.165	0.132	0.160	0.036	0.105	0.177	0.049	0.021	0.035	0.059	0.043	0.035	0.021	0.040	0.028	0.021	0.013	0.020

Fig. 1. Annual change in routine infant BCG vaccine coverage. Top: Change in annual number of routine infant BCG vaccines (grey squares) and live births (black diamonds). The number of live births has gradually decreased over the last 20 years. The number of BCG vaccines has fluctuated according to changes in the routine vaccination system. Bottom: Annual change in routine infant BCG vaccine coverage, represented by the number of BCG vaccines per number of live births. $^{*}p<0.05$, Mann–Whitney U test. [a]COVID-19 prevalence on March 29 (patients per million).

entire households, and ratio of workers in the primary, secondary and tertiary sectors of industry to entire working population were obtained from results of the national census in 2015.[5]

Statistical analyses

The Kolmogorov–Smirnov test revealed that the variables did not have a normal distribution. Therefore we performed non-parametric analyses to compare annual BCG vaccine coverage among prefectures and to examine the correlation of SARS-CoV-2 prevalence with BCG vaccine coverage and other related factors. The significance level was set at $p = 0.05$ for group comparisons and $p = 0.01$ for correlation analyses. All statistical analyses were performed using SPSS 16.0 J (IBM Japan, Tokyo, Japan).

Results

Table 1 depicts the prevalence of patients with COVID-19, SARS-CoV-2 PCR+ individuals, and deaths owing to COVID-19 in each prefecture. The prevalence of COVID-19 varied widely among the 47 prefectures. On March 29, no infections were detected in five prefectures (Iwate, Yamagata, Toyama, Tottori, and Shimane), whereas 33.30 individuals/million were diagnosed in Hokkaido. On April 24 and May 1, only Iwate had no infections. PCR+ individuals were the most prevalent in Tokyo on May 1 (298.08 individuals/million). The mortality rate was high in Fukui, Gunma, and Ishikawa prefectures (9.04, 7.68, and 5.25 deaths/million, respectively). The case fatality rate was high in Gunma, Aichi, and Ehime prefectures (10.27, 6.38, and 6.38 deaths/PCR+ individuals (%)).

The annual change in routine infant BCG vaccine coverage is shown in Fig. 1 and Table 2. BCG vaccine coverage was relatively low and variable among prefectures between 1999 and 2002. In eight prefectures coverage was less than 50%, and in Tokyo and Kanagawa less than 30% of the live births. In 2004, in accordance with the national policy on improving tuberculosis prevention and change in the target age of vaccination, the nationwide BCG vaccine coverage was 1.179 and that of Iwate was as high as 1.469. In 2006 and thereafter, the vaccine coverage was more than 50%, except for 42% in Miyagi in 2010. The vaccination coverage gradually stabilized, with all prefectures maintaining a greater than 90% coverage rate since 2013.

Fig. 1 shows a comparison of annual BCG vaccine coverage among the five prefectures with no COVID-19 infections and the top five prefectures with the highest COVID-19 prevalence (Hokkaido, Tokyo, Chiba, Oita, and Hyogo) on March 29, 2020. In 1999, 2000, 2001, 2002, 2004, and 2012, the BCG vaccine coverage of the five prefectures with no infections was significantly higher than that of the prefectures with a high prevalence of COVID-19 infections ($p<0.05$). Prior to 2005, the target age of vaccination was less than 4 years old; therefore, the vaccine coverage in 1999 was actually relevant to the generation born between 1995 and 1999.

The prevalence of patients with COVID-19, SARS-CoV-2 PCR+ individuals, and deaths owing to COVID-19 showed a significant negative correlation with BCG vaccine coverage in 2004, ratio of the elderly population (age 65 years or more), and the primary sector of industry, and a significant positive correlation to days from diagnosis of the first patient with COVID-19 to March 29

Table 2
Routine infant BCG coverage in each prefecture, 1998–2007.

Year	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
All Japan	0.965	1.005	0.948	0.969	0.974	0.969	1.179	0.936	0.895	1.000
Hokkaido	0.932	0.649	0.552	0.528	**0.500***	0.953	1.099	0.953	0.828	0.984
Aomori	0.973	1.008	0.929	0.881	0.967	1.014	1.462	0.613	0.830	0.990
Iwate	0.970	1.036	0.966	0.989	1.024	0.997	1.469	**0.472**	0.722	0.991
Miyagi	0.927	0.522	**0.463**	**0.460**	0.529	0.793	1.186	0.860	0.920	0.978
Akita	1.010	0.752	0.682	0.656	0.595	1.041	1.423	1.002	0.977	0.999
Yamagata	0.991	0.950	1.022	1.000	1.039	1.046	1.209	1.034	0.986	0.995
Fukushima	0.919	0.681	0.619	0.698	0.621	1.015	1.270	1.024	0.975	0.991
Ibaraki	0.849	0.981	0.966	0.903	0.976	0.948	1.249	1.015	0.806	1.004
Tochigi	0.959	0.777	0.719	0.706	0.757	0.995	1.382	0.970	0.847	0.965
Gunma	0.976	1.072	1.006	0.907	1.034	0.905	1.226	0.864	0.675	1.022
Saitama	0.937	1.000	0.901	0.969	0.825	0.982	1.146	1.036	0.768	0.953
Chiba	0.928	0.835	0.778	0.736	0.731	1.003	1.169	0.862	0.860	0.978
Tokyo	0.945	**0.336**	***0.289***	**0.342**	***0.285***	0.923	0.952	0.898	0.926	0.950
Kanagawa	0.982	**0.425**	**0.415**	***0.290***	***0.296***	0.999	1.024	0.973	0.926	1.000
Niigata	1.002	0.794	0.825	0.773	0.764	0.882	1.184	0.996	0.938	0.995
Toyama	0.891	0.701	0.668	0.712	0.693	1.044	1.399	1.908	0.916	0.916
Ishikawa	1.024	0.679	0.569	0.596	0.599	0.989	1.080	1.040	0.991	1.058
Fukui	0.991	1.060	0.981	1.000	1.015	1.022	1.462	0.960	0.634	1.009
Yamanashi	0.979	0.999	0.886	0.948	0.844	0.956	1.079	1.006	0.824	0.913
Nagano	0.990	0.853	0.779	0.802	0.847	1.011	1.483	0.892	0.857	0.985
Gifu	0.900	0.832	0.704	0.800	0.798	0.719	1.025	0.809	0.751	0.988
Shizuoka	0.979	0.669	0.734	0.744	0.703	1.019	1.241	0.990	1.004	0.988
Aichi	0.996	0.631	0.600	0.611	0.632	1.043	1.188	0.979	0.980	1.005
Mie	1.013	1.097	0.990	1.006	0.999	1.042	1.240	0.997	0.702	1.003
Shiga	1.037	0.978	1.028	0.960	1.005	1.037	1.328	0.812	0.910	0.990
Kyoto	1.002	**0.332**	**0.428**	**0.468**	**0.458**	0.992	1.175	0.947	0.938	1.425
Osaka	0.965	0.614	0.546	0.519	0.548	0.923	1.099	0.853	0.878	0.961
Hyogo	1.006	0.681	0.650	**0.493**	**0.469**	1.016	1.146	1.000	0.902	1.010
Nara	0.960	0.920	0.963	1.002	0.740	0.996	1.270	1.013	0.932	0.985
Wakayama	0.970	0.655	0.551	0.625	0.627	0.971	1.201	0.970	1.301	0.966
Tottori	1.014	1.149	0.930	0.650	1.009	0.657	1.195	1.027	0.980	0.880
Shimane	0.956	1.037	0.931	1.023	0.982	1.071	1.386	1.007	1.104	0.972
Okayama	0.902	0.636	**0.463**	**0.366**	**0.366**	1.015	1.220	0.895	0.950	0.985
Hiroshima	0.988	**0.415**	**0.413**	**0.336**	**0.312**	0.932	1.123	0.958	1.016	0.945
Yamaguchi	0.985	1.022	0.939	0.842	0.850	1.003	1.158	1.003	0.910	0.991
Tokushima	0.678	0.998	0.956	1.038	0.976	1.038	1.389	0.917	0.943	0.967
Kagawa	0.918	0.605	0.542	0.621	0.602	0.836	1.341	1.016	0.979	0.919
Ehime	0.997	1.111	0.649	0.641	0.646	1.053	1.249	1.039	0.991	0.987
Kochi	1.084	0.529	0.505	0.504	0.522	1.015	1.223	0.938	0.811	0.988
Fukuoka	0.985	0.528	**0.446**	**0.372**	0.515	0.854	1.195	0.751	0.772	1.252
Saga	1.020	1.058	0.966	0.984	1.018	0.913	1.277	1.147	0.977	0.990
Nagasaki	0.964	0.802	0.729	0.545	0.553	0.930	1.253	0.990	0.950	0.990
Kumamoto	0.993	0.576	0.545	0.543	0.582	1.026	1.401	0.994	0.945	0.972
Oita	0.944	0.694	**0.473**	**0.422**	0.681	1.009	1.275	0.501	0.968	0.960
Miyazaki	0.987	0.719	0.672	0.656	0.683	0.987	1.316	0.805	0.867	0.950
Kagoshima	1.148	0.684	0.655	0.685	0.663	1.079	1.387	0.972	0.951	0.978
Okinawa	0.927	0.885	0.926	0.925	0.932	1.016	1.451	0.880	0.963	0.967
Average	0.968	0.787	0.722	0.708	0.719	0.973	1.249	0.949	0.906	0.993

Bold indicate values <0.5, and bold italics indicate <0.3. *0.4997 before rounding.

(p<0.01) (Fig. 2, Table 3). Because the elderly population showed an inverse association with prevalence of SARS-CoV-2 infection, additional correlation analyses by age group were performed. A significant positive correlation was shown between the prevalence of SARS-CoV-2 infection and age groups 20–34 and 40–54 years (Fig. 3). As for occupation, workers in the tertiary sector of industry were significantly correlated with SARS-CoV-2 infection in a positive manner (Fig. 3) (Table 3).

Discussion

In this study, we evaluated the relationship between BCG vaccination and SARS-CoV-2 infection in Japanese patients with COVID-19 infection. To the best of our knowledge, this is the first study to demonstrate an impact of routine infant BCG vaccine coverage among younger people, especially those born between 1995 and 2004, on local COVID-19 spread in Japan. The current data are in accordance with the concept of silent spreaders in which asymptomatic or mild cases have a substantial role in the dissemination of SARS-CoV-2.[6] Moreover, our study findings suggest that infant BCG vaccination has a protective effect against mass infection.

Diagnosis of COVID-19 was made based upon the Infectious Disease Surveillance System in Japan, in accord with the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (the Infectious Diseases Control Law). Because in principle, the Act is applicable to individuals with flulike symptoms such as fever, cough, and fatigue, which are suggestive of SARS-CoV-2 infection, all patients officially notified on March 29 were symptomatic. Along with the disease spread, the Act has been applied to asymptomatic ones; the number of official notifications thereafter included PCR+ individuals both with and without clinical symptoms. The number of PCR+ individuals is lower than the actual number because of limited PCR testing in Japan; however, considering the relatively good correlation between the prevalence

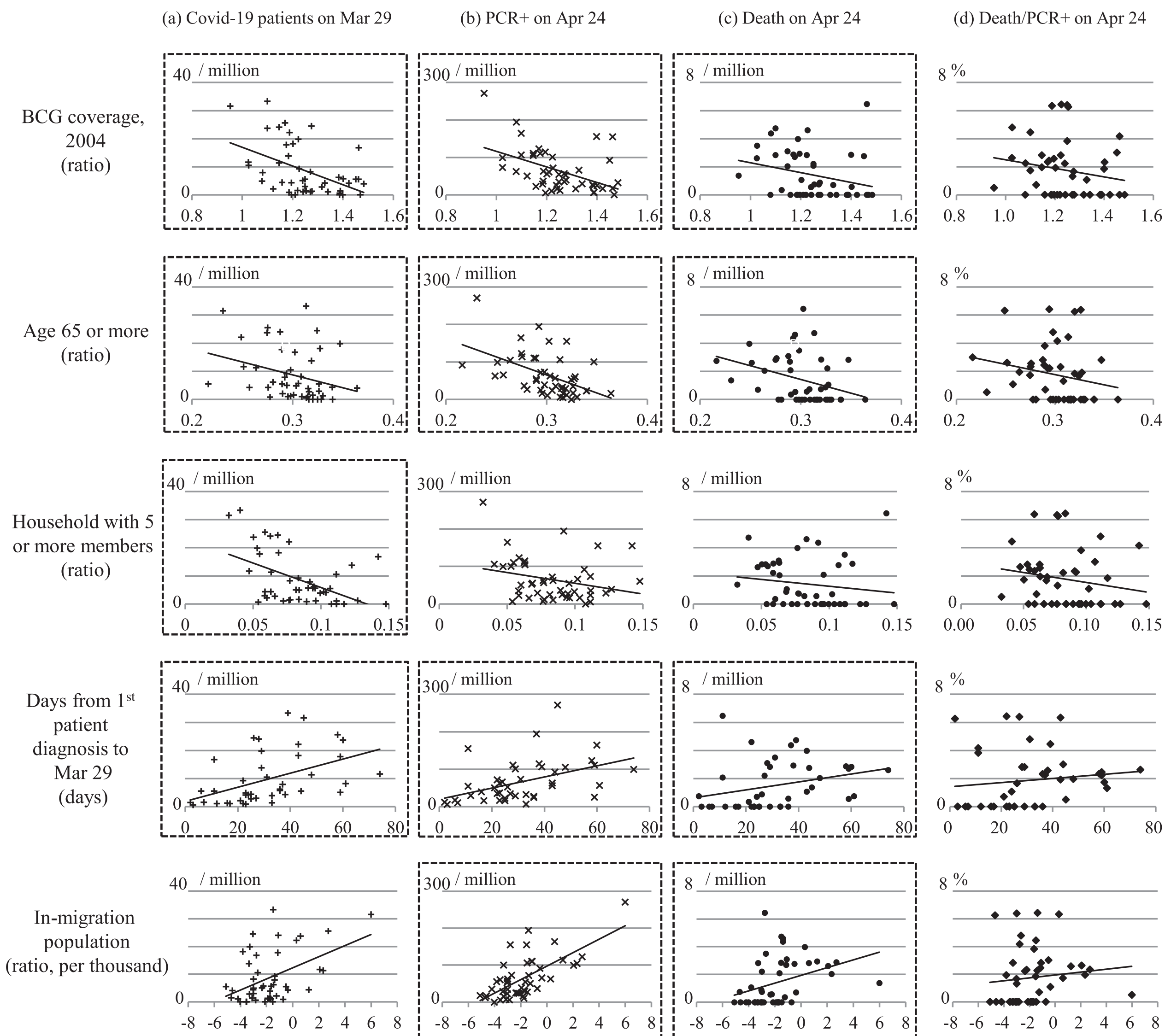


Fig. 2. Correlation between COVID-19 prevalence and related factors. Scatter plot of COVID-19 prevalence (ordinate) against related factors (abscissa). Prevalence of (a) patients with COVID-19 on March 29, (b) SARS-CoV-2 PCR+ individuals on April 24, and (c) deaths on April 24 showed significant negative correlation with BCG vaccine coverage in 2004, the population age 65 years or more, and workers in the primary sector of industry; and significant positive correlation with days from the first patient diagnosis with COVID-19 up to March 29. Dotted squares indicate significant correlation (Spearman's rank correlation, $p<0.01$). Regression lines are shown for reference.

of PCR+ individuals and the PCR positivity rate, this likely has little involvement in nonparametric analyses (Table 4). Nevertheless, this difference may cause inconsistent results for the case fatality rate among prefectures.

The significant negative correlation between COVID-19 infection and the population age 65 years and over suggests that in Japan, this population is irrelevant to disease spread. In contrast, the case fatality rate is high among those age 70 years or older (Fig. 4). Acute respiratory distress syndrome subsequent to SARS-CoV-2 respiratory infection is attributable to a high level of inflammatory cytokines, which increase with age, especially in men.[7,8] BCG vaccination induces trained immunity that enhances host defence mechanisms against nonspecific pathogens.[9-11] BCG-vaccinated neonates (BCG-Denmark 0.05 mL intradermally within 10 days of birth) showed increased interleukin 6 in an unstimulated state but decreased production of interleukins and chemokines following stimulation with pathogens.[12] This efficacy possibly contributed to the protection against SARS-CoV-2 spread, infection, and mortality in communities with high BCG vaccine coverage among younger people. In Japan, routine BCG vaccination has been the principal element in tuberculosis control. The incidence of tuberculosis in Japan has drastically decreased from 698.4 in 1951 to 17.7 per 100,000 in 2011.[13] After the introduction of BCG to the country in 1924, data on tuberculosis prevention and adverse event profiles had been accumulated mainly among young nurses or students.[14] Group BCG vaccination commenced in 1946 for young people in their teens and 20 s, and in 1949 for all citizens younger than 30 years old; vaccination was repeated each year until positive tuberculin skin test result was obtained.[14, 15] In 1949, a freeze-dried BCG vaccine that passed quality control assays replaced the previous liquid form.[15] A multiple puncture method was adopted in 1967, to avoid adverse skin reactions to intradermal vaccination.[4,14,16] In 1974, the timing of routine infant vaccination was set at less than 4 years old, followed by revaccination twice during the first year of elementary school and during the first or second year of junior high school after tuberculin skin test

Table 3
Correlation coefficient (Spearman's ρ) between SARS-CoV-2 infection and related factors.

	Prevalence (per million)					Deaths/PCR+ (%)	
	Patients with COVID-19 on Mar 29	PCR+ on Apr 24	Deaths on Apr 24	PCR+ on May 1	Deaths on May 1	On Apr 24	On May 1
BCG vaccine coverage (ratio)							
1998	0.028	−0.047	−0.021	−0.062	0.016	0.000	0.006
1999	−0.274	−0.306*	−0.189	−0.303*	−0.217	−0.064	−0.079
2000	−0.271	−0.254	−0.205	−0.254	−0.230	−0.115	−0.133
2001	−0.299*	−0.223	−0.254	−0.219	−0.276	−0.196	−0.208
2002	−0.324*	−0.268	−0.254	−0.268	−0.273	−0.185	−0.188
2003	−0.175	−0.162	−0.073	−0.156	−0.083	−0.031	−0.054
2004	−0.460**	−0.489**	−0.366**	−0.497**	−0.381**	−0.245	−0.264
2005	−0.278	−0.025	−0.121	−0.015	−0.140	−0.116	−0.141
2006	−0.332*	−0.261	−0.298*	−0.230	−0.285	−0.300*	−0.272
2007	0.183	0.161	−0.305*	0.151	0.303*	−0.374*	0.361*
2008	0.014	0.100	0.112	0.110	0.094	0.084	0.080
2009	−0.100	−0.037	−0.08	−0.036	−0.052	−0.160	−0.112
2010	0.033	−0.076	0.011	−0.072	0.009	0.045	0.020
2011	0.132	0.210	0.266	0.199	0.243	0.220	0.235
2012	−0.104	0.131	0.079	0.121	0.069	0.013	0.027
2013	−0.154	−0.036	−0.207	−0.048	−0.215	−0.196	−0.215
2014	−0.107	−0.074	−0.244	−0.089	−0.259	−0.205	−0.228
2015	0.089	0.137	0.217	0.127	0.195	0.201	0.213
2016	0.035	0.110	0.046	0.111	0.024	0.025	0.032
2017	0.207	0.121	0.164	0.124	0.150	0.157	0.169
Inhabitable area (km^2)	−0.003	−0.162	−0.098	−0.160	−0.148	−0.039	−0.085
Age (ratio,%)							
65 years or more	−0.382**	−0.537**	−0.436**	−0.519**	−0.413**	−0.340*	−0.302*
0–4 years	−0.048	0.068	0.136	0.066	0.102	0.129	0.083
5–9 years	−0.148	−0.109	0.073	−0.113	0.033	0.148	0.102
10–14 years	−0.209	−0.123	0.037	−0.138	−0.016	0.109	0.063
15–19 years	0.005	0.215	0.220	0.195	0.180	0.183	0.164
20–24 years	0.505**	0.678**	0.551**	0.663**	0.539**	0.383**	0.363*
25–29 years	0.430**	0.562**	0.462**	0.549**	0.445**	0.345*	0.307*
30–34 years	0.300*	0.471**	0.375**	0.464**	0.356*	0.284	0.243
35–39 years	0.210	0.321*	0.231	0.314*	0.205	0.160	0.113
40–44 years	0.383**	0.613**	0.504**	0.599**	0.485**	0.344*	0.317*
45–49 years	0.501**	0.654**	0.553**	0.643**	0.550**	0.390**	0.397**
50–54 years	0.546**	0.512**	0.400**	0.503**	0.399**	0.308*	0.318*
55–59 years	−0.185	−0.359*	−0.358*	−0.349*	−0.349*	−0.206	−0.187
60–64 years	−0.493**	−0.665**	−0.580**	−0.656**	−0.574**	−0.405**	−0.403**
65–69 years	−0.435**	−0.618**	−0.526**	−0.602**	−0.522**	−0.381**	−0.373*
70–74 years	−0.085	−0.229	−0.084	−0.218	−0.065	−0.107	−0.069
75–79 years	0.146	−0.055	0.030	−0.059	0.068	0.027	0.087
80–84 years	−0.337*	−0.579**	−0.475**	−0.561**	−0.450**	−0.364*	−0.328*
85 years or more	−0.492**	−0.593**	−0.509**	−0.581**	−0.483**	−0.407**	−0.383**
Household with 5 or more members (ratio)	−0.489**	−0.252	−0.323*	−0.250	−0.367*	−0.296*	−0.323*
Day/night population (ratio)	−0.130	0.081	−0.008	0.094	0.012	−0.103	−0.097
Days 1st diagnosis - Mar 29	0.606**	0.533**	0.432**	0.533**	0.452**	0.291	0.298
Inward population (ratio)	0.370*	0.642**	0.507**	0.638**	0.486**	0.339*	0.300*
Industry worker (%)							
Primary sector	−0.466**	−0.684**	−0.579**	−0.672**	−0.553**	−0.402**	−0.383**
Secondary sector	−0.136	0.032	−0.011	0.016	−0.047	−0.059	−0.067
Tertiary sector	0.400**	0.374**	0.385**	0.383**	0.404**	0.316*	0.309*

$^{*}p<0.05$, $^{**}p<0.01$.

screening.[14] In 1999, a state of emergency concerning tuberculosis was declared because gradual mitigation of tuberculosis prevention measures during previous periods brought about a resurgence of newly infected patients.[17] In 2003, revaccination was abandoned because of insufficient evidence of efficacy.[18] The target age of routine infant BCG vaccination was set at younger than 6 months old in 2005 and then at 1 year old in 2013. High COVID-19 mortality among elderly people may be owing to a lack of benefit received from immunization as routine BCG vaccination for infants using qualified freeze-dried BCG commenced in 1949, and BCG vaccination was not administered in those with a positive tuberculin skin test. Current younger generations born in the late 1990s and early 2000s, before establishment of the reinforced tuberculosis control system, have relatively low BCG vaccine coverage. It is possible that their parents, age around 50 years (considering mean age of the mother at the first childbirth was 28 years old in 2000[19]), represent the significant positive correlation with COVID-19 infection in these age groups.

Several studies have compared the incidence and severity of COVID-19 among countries with different BCG vaccination policies and found a protective effect of universal BCG vaccination, especially during the past 15 years, and high vaccination coverage in young people under 25 years of age.[20-22] A cohort study in Rhode Island in the United States also demonstrated the potential of BCG in preventing severe COVID-19 requiring hospitalization[23]; these findings are in accord with those of the present study. Two within-country studies from Israel and Germany failed to demonstrate the relevance of BCG vaccination to COVID-19 pre-

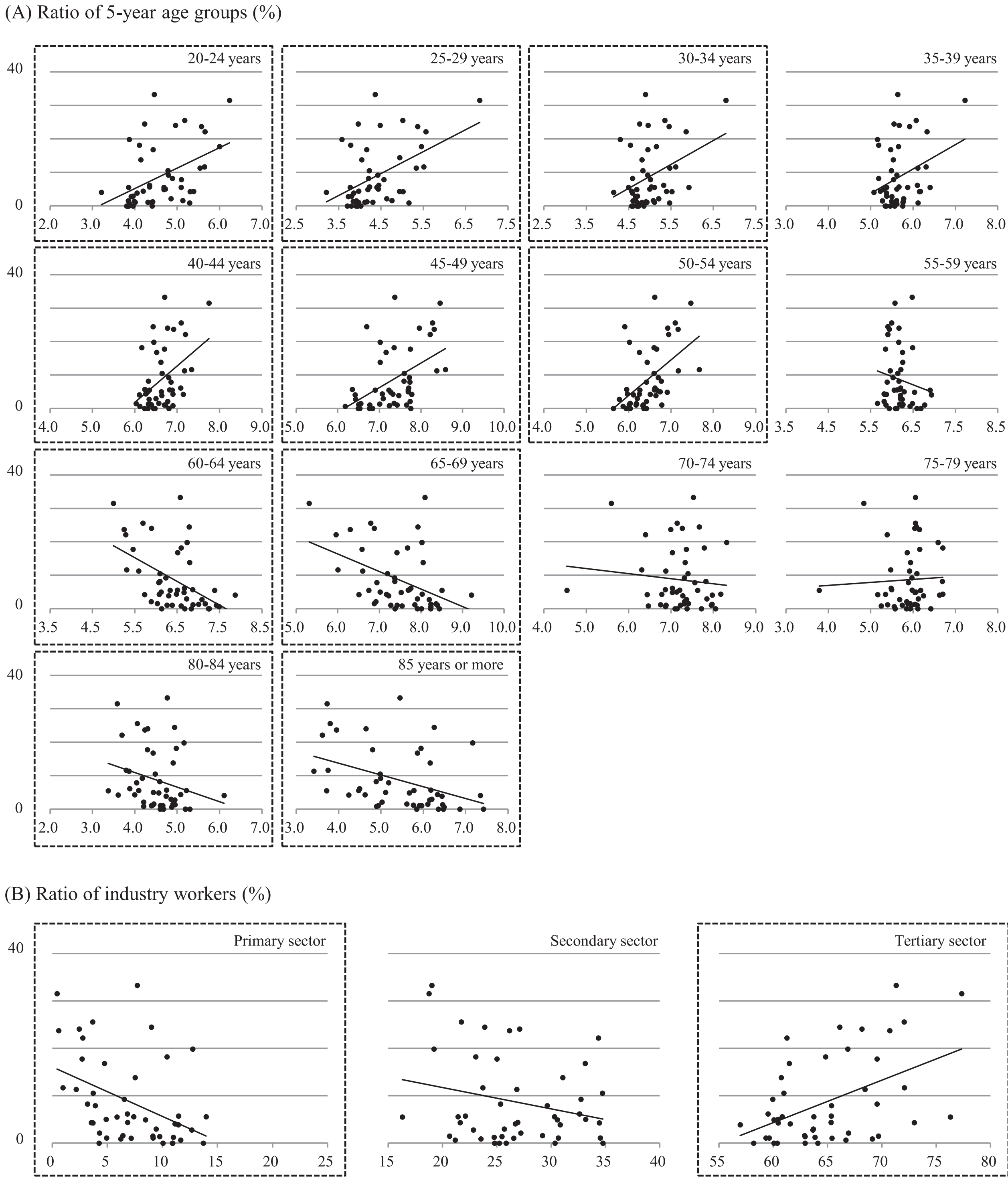


Fig. 3. Correlation between prevalence of patients with COVID-19 on March 29 and related factors. Scatter plot of the prevalence of patients with COVID-19 (ordinate) against related factors (abscissa). (A) Significant positive correlation of age groups 20–24, 25–29, 30–34, 40–44, 45–49 and 50–54 years with COVID-19 prevalence. (B) Workers in the tertiary sector of industry were significantly correlated with SARS-CoV-2 infection in a positive manner. Dotted squares indicate significant correlation (Spearman's rank correlation, $p<0.01$). Regression lines are shown for reference.

Table 4
Prevalence of PCR+ individuals (descending order), number of PCR tests conducted, and positivity rate on April 24 in each prefecture.

	(A) Prevalence of PCR+ (per million)	(B) Number of PCR testing (per million)	(C) Positivity ratio (%)
Tokyo	271.09	710.97	38.10
Ishikawa	194.23	1245.84	15.60
Osaka	164.30	782.37	19.20
Toyama	155.24	1795.24	8.60
Fukui	155.04	1696.38	9.10
Chiba	122.78	780.02	14.80
Fukuoka	114.35	1559.23	7.30
Kyoto	110.38	1394.83	7.90
Hyogo	110.32	1178.52	9.40
Hokkaido	106.32	1014.38	10.50
Saitama	104.64	803.41	13.00
Kochi	100.57	1832.86	5.50
Kanagawa	99.38	553.01	16.60
Okinawa	91.85	1184.39	7.80
Gifu	73.11	1137.71	6.40
Gunma	71.72	1246.93	5.80
Shiga	65.86	808.07	8.20
Aichi	62.89	832.16	7.60
Yamanashi	62.42	2352.51	2.70
Yamagata	60.55	1786.24	3.40
Nara	56.76	876.03	6.50
Wakayama	55.61	2701.60	2.10
Ibaraki	54.57	1401.11	3.90
Oita	52.45	2543.71	2.10
Hiroshima	50.41	1504.79	3.30
Saga	39.07	868.13	4.50
Miyagi	36.27	677.03	5.40
Fukushima	35.41	761.80	4.60
Ehime	34.76	741.12	4.70
Nagano	32.48	750.36	4.30
Kagawa	29.11	1483.37	2.00
Niigata	28.94	1109.08	2.60
Tochigi	27.24	859.71	3.20
Mie	25.13	922.95	2.70
Kumamoto	24.47	1492.89	1.60
Shimane	23.53	1102.94	2.10
Yamaguchi	22.63	888.32	2.50
Aomori	17.42	409.34	4.30
Akita	16.31	801.22	2.00
Shizuoka	16.12	646.62	2.50
Miyazaki	15.73	934.32	1.70
Nagasaki	11.93	1288.59	0.90
Okayama	10.54	548.47	1.90
Tokushima	6.79	524.46	1.30
Kagoshima	6.20	687.11	0.90
Tottori	5.36	1658.93	0.30
Iwate	0.00	225.62	0.00

Spearman's rank correlation between (A) and (B): $\rho=0.320$, $p<0.05$, between (A) and (C): $\rho=0.912$, $p<0.001$.

vention; however, those studies do not contradict our study findings considering that universal immunization was discontinued in these countries in 1982 and 1990, respectively, and that the number of asymptomatic silent spreaders could not be evaluated.[24, 25]

Conclusions

In summary, the current study demonstrated that routine infant BCG vaccine coverage in young people showed a protective effect against local COVID-19 spread in Japan. The possible relevance of infant BCG vaccination to high mortality among elderly patients with COVID-19 should be elucidated.

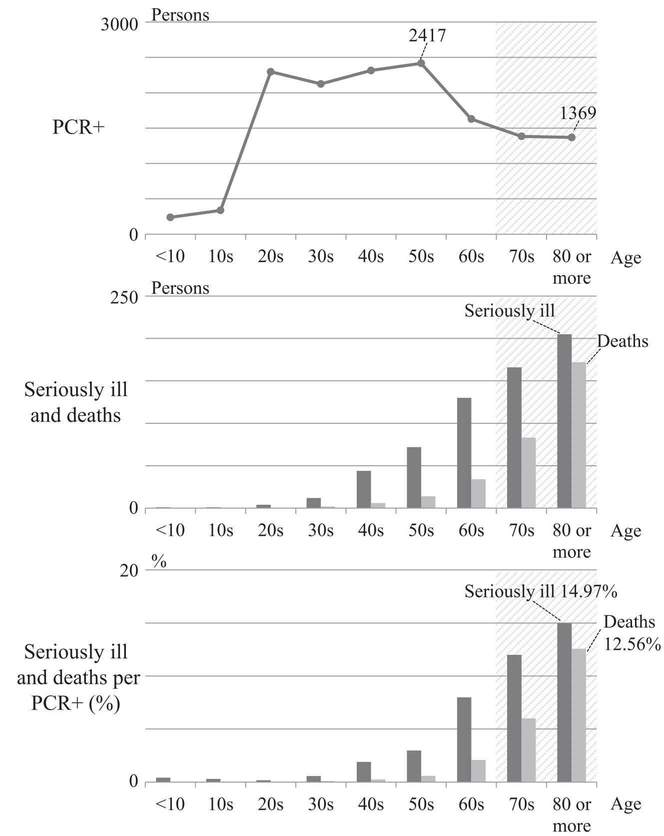


Fig. 4. Number of PCR+ individuals (top), seriously ill patients and deaths owing to COVID-19 (middle), and their proportions (bottom) in each age group on May 1. A drastic increase in case fatality rate was observed with age, especially among individuals age 70 years or older. Shaded squares show age groups born before commencement of routine BCG vaccination for infants using qualified freeze-dried BCG.

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Declaration of Competing Interest

None.

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